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# The VHL-HIF Signaling in Renal Cell Carcinoma: Promises and Pitfalls

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## 1. Introduction

Renal cell carcinoma (RCC) is the third most common genitourinary cancer behind prostate and bladder cancer, accounting for 3% of all adult malignancies (Curti, 2004). It is a highly metastatic and heterogeneous disease with at least 16 histologic subtypes (Eble et al., 2001; Lopez-Beltran et al., 2006), among which clear cell (70-80%), papillary (10-15%) and chromophobe (5%) are the most common (Curti, 2004). Up to 25% of patients with RCC have distant metastases at presentation. Another 50% develop metastases or local recurrence during follow-up, despite treatment of the primary tumor (Thyaviahally et al., 2005). The average survival, following metastatic RCC, is about 4 months, and only 10% of patients survive for one year. The global incidence of RCC per year is close to 300000, with a male to female ratio of 3:2 and an estimated mortality of approximately 100000 (Arai&Kanai, 2010; Ferlay et al., 2010). The incidence of RCC has been rising steadily, probably because of incidental findings from imaging techniques performed for other reasons. It can occur at any age, but is most frequently diagnosed in the 40-70 year old group (Eble et al., 2001; Pascual & Borque, 2008; Arai&Kanai, 2010).

Well before the advent of the modern era of genetics and molecular biology, surgeons and pathologists were aware of the hyper-vascular nature of RCC (Corn, 2007). The subsequent isolation of the von Hippel-Lindau (VHL) gene in 1993 led to the important discoveries that aberrant VHL is the most important risk for RCC and that VHL negatively regulates the hypoxia inducible factor (HIF) and thus the downstream angiogenesis pathway thereby engendering increased vascularity. In this chapter, we will focus on the role of the VHL-HIF pathway in RCC, advancements in novel therapeutics targeting this pathway and future directions.

## 2. Von Hippel-Lindau syndrome

VHL disease, commonly known as the VHL syndrome, is named after the German ophthalmologist Eugene von Hippel, and the Swedish neuropathologist Arvid Lindau, who

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in the early 1900s, described highly vascularised tumors of the retina and the central nervous system (Kim&Kaelin, 2004; Ohh, 2006). VHL syndrome is the result of germ line mutations in VHL, a tumor-suppressor gene located on chromosome 3p25 (Seizinger et al., 1988; Kim&Kaelin, 2004; Clark, 2009; Gossage&Eisen, 2010). It affects 1 in 35,000 individuals and is associated with the development of tumors in multiple organs, including the brain, spinal cord, pancreas, adrenal gland, epididymis (in males), broad ligament (in women) and kidneys (Lonser et al., 2003; Kim&Kaelin, 2004; Grubb et al., 2005; Clark, 2009). Individuals with VHL syndrome carry one wild type VHL allele and one faulty allele. Tumors develop only after the spontaneous somatic loss (loss of heterozygosity [LoH]) or inactivation, or both, of the remaining wild type. Thus, at cellular level, VHL syndrome can be considered as an autosomal recessive disease, whilst clinically, it manifests more like an autosomal dominant disease because the inactivation of the wild type allele is almost guaranteed (Ohh&Kaelin, 2003; Ohh, 2006). Apart from LoH and mutations, hypermethylation of the VHL promoter regions can prevent the wild-type VHL gene from expressing its functional tumor suppressor protein pVHL (Kim&Kaelin, 2004). The VHL gene is mutated in 50-80% (Weiss&Lin, 2006; Arai&Kanai, 2010) and hypermethylated in 19% (Herman et al., 1994; Arai&Kanai, 2010) of sporadic clear cell RCC. Clear cell RCC is the leading cause of death in patients with VHL mutation (Maher et al., 1990; Clark, 2009; Gossage&Eisen, 2010).

The VHL gene, which was isolated in 1993 (Latif et al., 1993), has three exons and encodes for two mRNA transcripts that are translated into three types of pVHL (Ohh&Kaelin, 2003; Ohh, 2006). The first VHL mRNA transcript that contains all three exons, is translated into a larger 213 amino acid protein of approximately 24-30 kDa (pVHL<sub>30</sub>), and a smaller 160 amino acid protein of approximately 18-19 kDa (pVHL<sub>19</sub>) due to alternative translation initiation (Iliopoulos et al., 1998; Schoenfeld et al., 1998; Blankenship et al., 1999; Safran&Kaelin, 2003). In the early days, both pVHL<sub>30</sub> and pVHL<sub>19</sub> were considered to be tumor suppressors (Iliopoulos et al., 1995; Ohh, 2006). However, further studies have cast doubt on the tumor suppressive role of pVHL<sub>19</sub> (Ohh, 2006). Generally, the term 'pVHL' is used to refer to both isoforms (Kim&Kaelin, 2004; Kaelin, 2007). The second VHL mRNA transcript lacks exon 2 due to alternative splicing. Literature on this isoform is scant, although RCCs that exclusively produce this shorter VHL mRNA transcript have been identified (Gnarra et al., 1996; Safran&Kaelin, 2003; Ohh, 2006).

pVHL consists of  $\alpha$  and  $\beta$  domains (Fig.1), which are essential for its tumor suppressor activities (Stebbins et al., 1999; Kaelin, 2002). pVHL forms complexes with elonginB, elonginC, Rbx1, and Cullin 2 to form an E3 ubiquitin ligase complex (Stebbins et al., 1999; Ohh et al., 2000; Tanimoto et al., 2000; Kaelin, 2002; Kaelin, 2005a; Kaelin, 2005b; Gossage&Eisen, 2010). The  $\alpha$  domain binds to elongin C and the  $\beta$  domain interacts with hydroxylated prolines of HIF (Fig.1). This complex has multiple functions, which can be broadly classified into HIF-independent and HIF-dependent. The HIF-independent functions include maintenance of primary cilia (Hergovich et al., 2003; Baldewijns et al., 2010), assembly of extracellular fibronectin matrix (Guo et al., 2009), regulation of apoptosis (Guo et al., 2009), epithelial mesenchymal transition (EMT) (Koochekpour et al., 1999; Hara et al., 2006), and transcriptional regulation (Yuen et al., 2007; Mikhaylova et al., 2008; Baldewijns et al., 2010). The best studied role is its HIF-dependent function in RCC, which is the degradation of HIF (Ohh, 2006; Baldewijns et al., 2010; Gossage&Eisen, 2010).

### 3. Hypoxia-inducible factor

A hypoxic tumor microenvironment is one of the characteristics of solid tumors. Cells undergo a variety of adaptive changes that will facilitate their survival under hypoxic conditions. One such change at the molecular level is the activation of the hypoxia-sensitive transcription factor, HIF. HIF is a heterodimer consisting of two subunits:  $\alpha$  and  $\beta$  (Wang et al., 1995; Kaluz et al., 2008). The  $\beta$  subunit, also known as aryl hydrocarbon receptor nuclear translocator (ARNT), is constitutively expressed and is independent of intracellular oxygen tension. The oxygen-sensitive  $\alpha$  subunit, which has three further subunits, HIF-1 $\alpha$ , HIF-2 $\alpha$ , and HIF-3 $\alpha$ , is also constitutively expressed, but is rapidly degraded under normoxic conditions (Semenza, 1999; Huang&Bunn, 2003; Maynard et al., 2003; Maynard&Ohh, 2004; Kaluz et al., 2008; Baldewijns et al., 2010). At least two mechanisms that negatively regulate the stability of HIF- $\alpha$  under normoxia have been recognized: oxygen-dependent prolyl hydroxylation and asparaginyl hydroxylation (Lando et al., 2002a; Lando et al., 2002b; Ohh, 2006).

HIF-1 $\alpha$  and HIF-2 $\alpha$  contain an N-terminal transactivation domain (NTAD), a C-terminal transactivation domain (CTAD) and an oxygen-dependent degradation domain (ODDD) [Fig.1] (Pugh et al., 1997; Sang et al., 2002; Baldewijns et al., 2010). The ODDD has a stretch of proline residues. HIF-3 $\alpha$  lacks the transactivation domain and has many splice variants. Under normoxic conditions, the proline residues within the ODDD of HIF- $\alpha$  are hydroxylated by prolyl hydroxylases (PH) at positions 402 and 564 (Ivan et al., 2001; Jaakkola et al., 2001; Schofield&Ratcliffe, 2005; Koivunen et al., 2007; Kaluz et al., 2008; Baldewijns et al., 2010). The pVHL-E3 ubiquitin ligase complex binds to the hydroxylated HIF- $\alpha$  through the  $\beta$  domain of pVHL and enables polyubiquitination. The polyubiquitinated HIF- $\alpha$  is degraded by the 26S proteasome (Maxwell et al., 1999; Ohh et al., 2000; Tanimoto et al., 2000; Jaakkola et al., 2001; Baldewijns et al., 2010). While the prolyl hydroxylation enables the binding of pVHL to HIF- $\alpha$  and its eventual degradation, the asparaginyl hydroxylation prevents the transcriptional activation of HIF target genes (Dames et al., 2002; Freedman et al., 2002). For transcriptional activity, HIF- $\alpha$  requires the recruitment of p300/CBP transcriptional coactivators (Arany et al., 1996). The CTAD has a conserved C-terminal asparagine. In normoxia, the factor inhibiting HIF-1 (FIH-1), an oxygenase, hydroxylates asparagine at position 803, which diminishes the recruitment of p300/CBP to HIF- $\alpha$  (Freedman et al., 2002) leading to the transcriptional downregulation of HIF responsive elements (Mahon et al., 2001; Dames et al., 2002; Lando et al., 2002a; Lando et al., 2002b).

In hypoxia, the activity of prolyl hydroxylases and FIH-1 are reduced, leading to the inhibition of proline and asparaginyl hydroxylation, respectively. In the absence of a functional pVHL, the binding of the pVHL-E3 ubiquitin ligase complex to HIF- $\alpha$  and the subsequent polyubiquitination and degradation of HIF- $\alpha$  are inhibited even under normoxic conditions. Both events lead to the stabilization and accumulation of HIF- $\alpha$  in cells. As a result, HIF- $\alpha$  is translocated to the nucleus, where it dimerizes with HIF- $\beta$ . The HIF- $\alpha$ /HIF- $\beta$  heterodimer binds to hypoxia-responsive elements (HRE) of the DNA, recruits p300/CBP to the CTAD and transactivates over 60 hypoxia-inducible genes of which, vascular endothelial growth factor (VEGF) (angiogenesis), transforming growth factor alpha (TGF- $\alpha$ ) and epidermal growth factor receptor (EGFR) (proliferation), carbonic anhydrase IX (CAIX)

(pH regulation), erythropoietin (EPO) (erythropoiesis), e-cadherin (EMT) and glucose transporter-1 (GLUT-1) (glucose metabolism) have attracted much attention (Ohh, 2006; Clark, 2009; Baldewijns et al., 2010). Because of the defective VHL-HIF-VEGF pathway, RCC is considered to be one of the most hypervascularized tumors. Hence, it is not surprising that considerable research in the past decade has focused on the angiogenic pathway, which led to the development of some promising novel therapeutics.

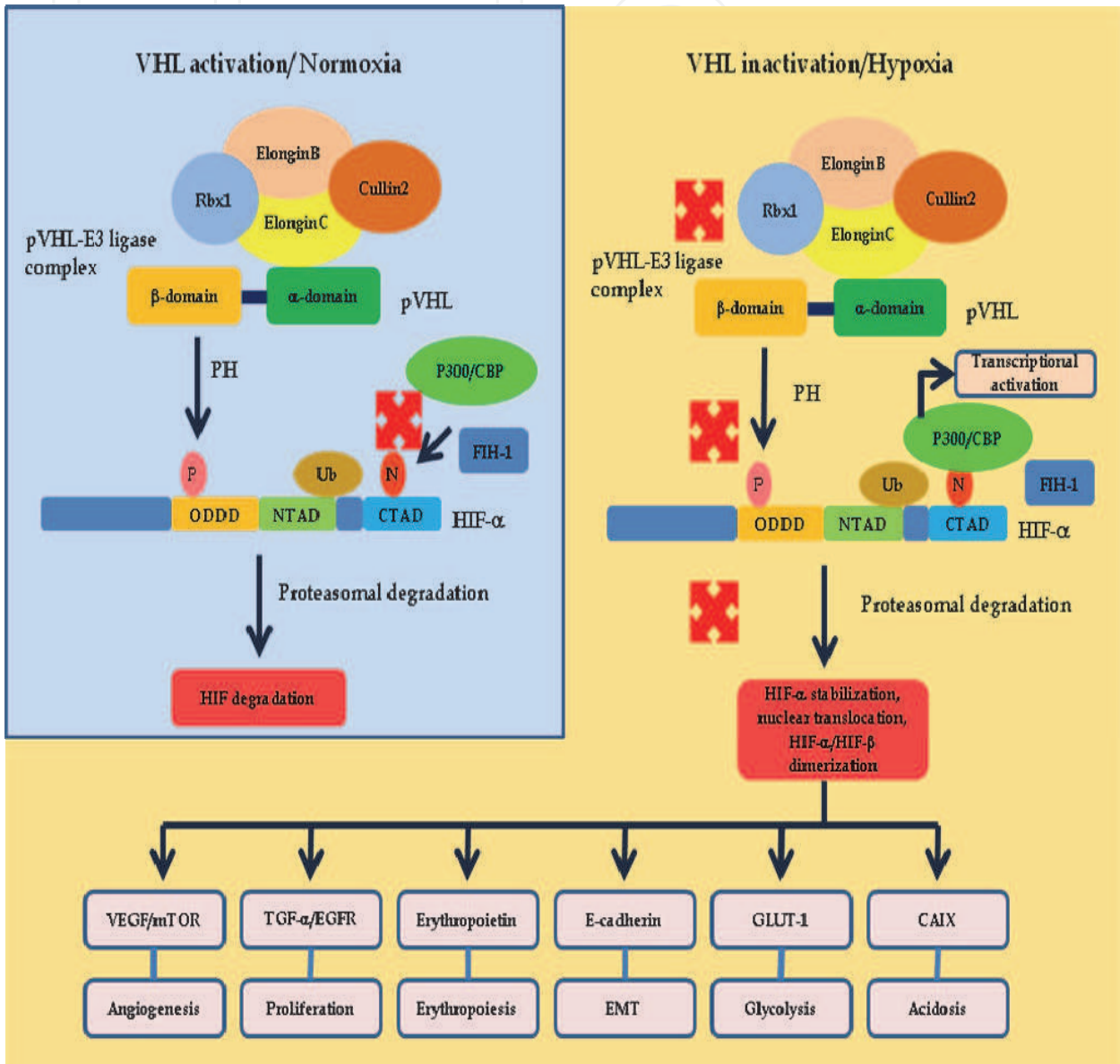


Fig. 1. The von Hippel-Lindau-Hypoxia Inducible Factor (VHL-HIF) pathway. The details are given in text. In brief, under active VHL and normoxic conditions, HIF is degraded. When the VHL gene is inactive due to mutations or hypermethylation, HIF is stabilized, translocated to the nucleus and activates the transcription of over 60 hypoxia-responsive molecules that are involved in oncogenesis and tumor progression. Only selected molecules and their alleged roles in tumor progression that are discussed in this chapter are shown. X, represents inhibition or inactivation. N, asparagine; P, proline; PH, prolyl hydroxylases; Ub, ubiquitination.



## 4. VHL inactivation and HIF-induced hypoxia responsive genes

### 4.1 Vascular endothelial growth factor – mammalian target of rapamycin

Of the many HIF-regulated angiogenic molecules, VEGF is perhaps the most studied - not only in RCC but also cancers in general. In humans, the VEGF system consists of five secreted ligands, namely VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor-1 (PlGF) and three receptor tyrosine kinases, VEGF-R1 (flt-1), VEGF-R2 (flk1 in the mouse, KDR in the human), and VEGF-R3 (flt4) (Carmeliet, 2005; Hicklin&Ellis, 2005; Tammela et al., 2005; Cebe-Suarez et al., 2006; Donovan&Kummar, 2006; Roy et al., 2006; Thurston&Kitajewski, 2008; Clark, 2009; Stuttfeld&Ballmer-Hofer, 2009; Bates, 2010). VEGF-R1 and VEGF-R2 are predominantly expressed in vascular endothelial cells and VEGF-R3 in lymphatic endothelial cells (Tammela et al., 2005; Thurston&Kitajewski, 2008). Hence, VEGF-R1 and VEGF-R2 are thought to be more important for angiogenesis and VEGF-R3 for lymphangiogenesis (Donovan&Kummar, 2006; Clark, 2009). The binding of the ligands to the receptors is an essential step in the initiation of the VEGF signaling. Generally, VEGF-R1 binds to VEGF-A, VEGF-B and PlGF; VEGF-R2 binds to VEGF-A, VEGF-C and VEGF-D and VEGF-R3 to VEGF-C and VEGF-D (Cebe-Suarez et al., 2006; Stuttfeld&Ballmer-Hofer, 2009). The receptor-ligand binding promotes conformational changes, followed by phosphorylation of specific tyrosine residues of the receptor (Cebe-Suarez et al., 2006; Stuttfeld&Ballmer-Hofer, 2009). Subsequently, a variety of downstream signaling pathways is activated, of which the most studied are the RAF-MEK-ERK series of kinases and the phosphatidylinositol-3 kinase-protein kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway (Clark, 2009; Banumathy&Cairns, 2010). Increased mTOR, which itself is the result of HIF activation secondary to VHL loss, can in turn lead to an increase in HIF thereby maintaining a positive feedback loop that exacerbates the deleterious effects of VHL inactivation (Cho et al., 2007; Clark, 2009; Banumathy&Cairns, 2010). Both pathways predominantly up-regulate a variety of pro-angiogenic factors, thereby imparting a hyper-angiogenic phenotype to RCC.

There is considerable evidence demonstrating that VEGF is significantly elevated in RCC, with some studies reporting its up-regulation in up to 96% of RCC (Takahashi et al., 1994). There is a direct correlation between VEGF expression, tumor microvascular density, disease progression and metastasis of RCC (Takahashi et al., 1994; Zhang et al., 2002; Fukata et al., 2005; Baldewijns et al., 2007; Rioux-Leclercq et al., 2007; Patard et al., 2009). Apart from VEGF, RCC is reported to over-express several potent pro-angiogenic factors, including basic fibroblast growth factor (bFGF) (Cenni et al., 2007), PlGF (Takahashi et al., 1994), platelet-derived growth factor (PDGF) (Xu et al., 2005a), epidermal growth factor (EGF) (Kedar et al., 2002), the interleukins IL-6 (Angelo et al., 2002) and IL-8 (Konig et al., 1999), leptin (Horiguchi et al., 2006b; Horiguchi et al., 2006a) and various chemokines (Slaton et al., 2001; Fukata et al., 2005).

Hence, it is not surprising that the past decade has placed much emphasis on HIF-regulated downstream pathways, especially angiogenesis. This has resulted in the development of many clinically available novel chemotherapeutic agents. They can be broadly categorized as VEGF inhibitors, multiple tyrosine kinase inhibitors and mTOR inhibitors. The most successful VEGF inhibitor is the humanized VEGF-neutralizing antibody, bevacizumab. Bevacizumab is thought to exert its anti-angiogenic activity by acting against the angiogenic endothelial cells surrounding the tumor rather than the tumor *per se* thus blocking the

supply of oxygen and nutrients to the tumors (Ellis&Hicklin, 2008; Ainsworth et al., 2009; Banumathy&Cairns, 2010). The clinically available multiple tyrosine kinase inhibitors are sunitinib, sorafenib, pazopanib and axitinib. As summarized in Table 1, they target multiple tyrosine kinase receptors neutralizing the downstream signaling pathways activated by ligand-receptor binding, as discussed above. Two of the most successful mTOR inhibitors are temsirolimus and everolimus. Both are rapamycin analogues and bind to FK506-binding protein 12 (FKBP12), which in turn binds to mTOR leading to the inhibition of the PI3K/Akt/mTOR pathway (Thomas et al., 2006; Abraham&Gibbons, 2007; Ainsworth et al., 2009; Banumathy&Cairns, 2010). In addition, temsirolimus has been shown to have a direct inhibitory effect on HIF- $\alpha$  and VEGF (Del Bufalo et al., 2006; Motzer et al., 2008; Banumathy&Cairns, 2010; Houghton, 2010).

Drug	Target receptors	Reference
Sunitinib	VEGFR1, VEGFR2, VEGFR3, PDGFR- $\alpha$ , PDGFR- $\beta$ , FLT3, c-KIT, RET	(Mendel et al., 2003; Faivre et al., 2006; Ainsworth et al., 2009; Banumathy&Cairns, 2010)
Sorafenib	VEGFR-2, PDGFR- $\beta$ , c-KIT, Raf-1	(Wilhelm&Chien, 2002; Wilhelm et al., 2004; Ainsworth et al., 2009)
Pazopanib	VEGFR1, VEGFR2, VEGFR3, PDGFR- $\alpha$ , PDGFR- $\beta$ , c-KIT	(Kumar et al., 2007; Ainsworth et al., 2009; Banumathy&Cairns, 2010; Sternberg et al., 2010)
Axitinib	VEGFR1, VEGFR2, VEGFR3, PDGFR- $\beta$ , c-KIT,	(Rugo et al., 2005; Rixe et al., 2007)

Table 1. Clinically available multiple tyrosine kinase inhibitors for metastatic RCC (Bullock et al., 2010)

4.2 Transforming growth factor- $\alpha$  and epidermal growth factor receptor

TGF- $\alpha$  is an autocrine mitogen for fibroblasts and epithelial cells. It has structural and functional homology to EGF (Derynck, 1986; Everitt et al., 1997). TGF- $\alpha$  is thought to mediate its biological effects through the binding of EGFR, which is a family of four closely related cell membrane receptors, EGFR (HER1; ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) (Higashiyama et al., 2008; Pu et al., 2009). These receptors are transmembrane glycoproteins with an extracellular ligand-binding domain and an intracellular tyrosine kinase domain (Higashiyama et al., 2008; Pu et al., 2009). Ligand-binding to the extracellular domain of EGFR activates tyrosine kinase, resulting in autophosphorylation of EGFR and subsequent signal transduction leading to cell cycle progression, inhibition of apoptosis, induction of angiogenesis, promotion of invasion and metastasis, and other oncogenic activities (Derynck, 1986; Everitt et al., 1997; Gunaratnam et al., 2003; Black&Dinney, 2008; Lee et al., 2008; Uberall et al., 2008; Pu et al., 2009). TGF- $\alpha$ /EGFR activation in RCC is either independent of, or dependent on the VHL status. While the mechanisms behind VHL-independent activation have not been fully elucidated, the VHL-dependent TGF- $\alpha$ /EGFR follows the classical pattern of HIF-1 up-regulation secondary to loss of VHL function (de

Paulsen et al., 2001; Gunaratnam et al., 2003; Lee et al., 2008). It has been suggested that TGF- $\alpha$  overproduction secondary to VHL deficiency is the consequence of HIF activation and that such activation establishes an autocrine TGF- $\alpha$ /EGFR stimulatory system leading to the oncogenic transformation of normal renal epithelial cells and the formation of RCC (Ishikawa et al., 1990; Atlas et al., 1992; Yoshida et al., 1994; Everitt et al., 1997; de Paulsen et al., 2001; Gunaratnam et al., 2003; Pelletier et al., 2009; Pu et al., 2009). For example, transgenic expression of TGF- $\alpha$  in mice leads to the formation of multiple renal cysts reminiscent of pre-neoplastic lesions of the human kidney, whilst the re-introduction of wild type VHL inhibits TGF- $\alpha$  expression and cyst formation (Lowden et al., 1994; Everitt et al., 1997; Knebelmann et al., 1998; de Paulsen et al., 2001; Kaelin, 2002; Gunaratnam et al., 2003).

Many studies have reported the over expression of TGF- $\alpha$  and EGFR in RCC (Freeman et al., 1989; Gomella et al., 1989; Mydlo et al., 1989; Sargent et al., 1989; Petrides et al., 1990; Lager et al., 1994; Yoshida et al., 1994; Uhlman et al., 1995; Everitt et al., 1997; Yoshida et al., 1997; Ramp et al., 2000; Merseburger et al., 2005; Lee et al., 2008; Pelletier et al., 2009; Pu et al., 2009). The expression pattern of TGF- $\alpha$  in RCC is such that it has been identified as an ideal candidate for immunotherapy (Pelletier et al., 2009). The prognostic association between over-expression of EGFR in RCC, and development of the cancer is controversial. Two distinct patterns of EGFR expression have been observed: a) cytoplasmic in normal renal cells, and b) membranous in RCC. These observations suggest that it is not just the over expression of EGFR, but the location of its over-expression that determines prognosis. Accordingly, RCC patients with positive membranous EGFR expression may have a poorer survival outcome when compared with those with negative expression of membranous EGFR (Pu et al., 2009). However, a previous study casts doubt on this hypothesis (Kallio et al., 2003).

Some studies have explored the therapeutic efficiency of EGFR inhibitors, either as single agents or in combination, with a success rate of around 10% (Motzer et al., 2003; Dawson et al., 2004; Rowinsky et al., 2004; Jermann et al., 2006; Ravaud et al., 2008; Gordon et al., 2009; Pu et al., 2009). Interestingly however, results of anti-EGFR therapy in other cancers show a lack of correlation between EGFR expression and response to therapy, suggesting that differential intracellular signaling events rather than the mere expression of EGFR may also play significant roles in predicting response to anti-EGFR therapy (Marks et al., 2008; Gordon et al., 2009). Furthermore, RCC cells with wild type VHL have been shown to be more sensitive to anti-EGFR treatment than those with mutated VHL (Perera et al., 2000; Gordon et al., 2009).

### 4.3 Erythropoietin

Paraneoplastic erythrocytosis is a salient feature of many cancers, including RCC in which about 5% of patients are polycythemic (Wiesener et al., 2002; Wiesener et al., 2007; Papworth et al., 2009). In adults, the kidney is the major source of EPO. EPO regulates erythropoiesis and is the only hematopoietic cytokine whose production is regulated by hypoxia (Lacombe&Mayeux, 1999; Fandrey, 2004; Michael et al., 2007; Wiesener et al., 2007). Although RCC is thought to arise from proximal tubular epithelial cells (PTEC), normal PTEC do not express detectable levels of EPO even under hypoxic conditions (Wiesener et al., 2002; Wiesener et al., 2007). This pointed towards the role of molecular mechanisms that transform a non-EPO expressing PTEC to an EPO-expressing RCC, leading to the



identification of the link between VHL mutation and the subsequent HIF-mediated EPO upregulation in RCC (Da Silva et al., 1990; Noguchi et al., 1999; Wiesener et al., 2002; Pastore et al., 2003; Lee et al., 2005; Wiesener et al., 2007; Rad et al., 2008; Papworth et al., 2009). Enhanced expression of EPO and its receptor EPOR has been reported in cultured RCC cells and in patient samples, the reported prevalence ranges from 33 - 84% (Murphy et al., 1970; Hagiwara et al., 1984; Da Silva et al., 1990; Ljungberg et al., 1992; Noguchi et al., 1999; Wiesener et al., 2002; Sakamoto et al., 2003; Lee et al., 2005; Michael et al., 2007; Wiesener et al., 2007; Papworth et al., 2009).

Although 33-84% of the RCC patients have elevated plasma level of EPO, only 5% of them are polycythemic (Kazal&Erslev, 1975; Ljungberg et al., 1992; Michael et al., 2007; Wiesener et al., 2007; Papworth et al., 2009). The lack of correlation between paraneoplastic EPO production and paraneoplastic erythrocytosis has led to the suggestion that other cancer-related factors can counterbalance the effect of increased EPO. One of the well studied factors is the reduced iron availability and the resultant anemia in cancer patients. Since recombinant human EPO (rhEPO) is frequently used to treat anemia in patients with cancer, the presence of EPOR in RCC has raised concern (Lai&Grandis, 2006; Papworth et al., 2009). As EPOR is over-expressed in RCC, and EPO exerts its effects through its binding of EPOR, exogenous rhEPO could enhance tumor aggressiveness as reported in breast and head and neck cancers (Henke et al., 2003; Leyland-Jones et al., 2005; Wiesener et al., 2007). Furthermore, EPO has been shown to reduce cisplatin-induced apoptosis in cultured RCC cells (Li et al., 2007). In contrast, EPO sensitized RCC cell lines to vinblastin and daunorubicin-induced apoptosis (Carvalho et al., 2005).

#### 4.4 E-cadherin

Cell-cell adherence, mediated by intercellular junctional complexes, plays an important role in tissue formation and maintenance of cell phenotypes. Intercellular junctional complexes are composed of tight junctions, adherence junctions and desmosomes (Cavallaro & Christofori, 2004; Krishnamachary et al., 2006; Migita et al., 2008). E-cadherin, a transmembrane glycoprotein, is the principal component of adherence junctions and desmosomes in epithelial cells (Cavallaro&Christofori, 2004; Krishnamachary et al., 2006). The extracellular domain of E-cadherin mediates cell-cell adherence through homophilic interaction with the E-cadherin of adjacent cells, whereas the intracellular domain binds with the cytoskeleton *via* a protein complex containing  $\alpha$ -,  $\beta$ - and  $\gamma$ -catenins (Behrens et al., 1989; Cavallaro&Christofori, 2004; Krishnamachary et al., 2006; Russell&Ohh, 2007). EMT is the hallmark of many cancers, in which E-cadherin-mediated cell-cell adherence is lost and the cells attain hyper-proliferative, invasive and metastatic properties (Behrens et al., 1989; Thiery, 2002; Krishnamachary et al., 2006). While the reasons for loss of E-cadherin in cancers are undoubtedly multifactorial, many studies have shown a direct role of VHL in regulating E-cadherin expression in RCC (Esteban et al., 2006; Krishnamachary et al., 2006; Evans et al., 2007; Russell&Ohh, 2007).

The loss of VHL in turn leads to a loss or significant downregulation of E-cadherin and its re-introduction restores E-cadherin expression in RCC (Esteban et al., 2006; Krishnamachary et al., 2006; Russell&Ohh, 2007). Further reports of E-cadherin loss in pre-malignant foci of VHL patients has led to the suggestion that E-cadherin loss is an early step in the pathogenesis of RCC, attributed to VHL inactivation (Esteban et al., 2006; Russell&Ohh,

2007). In line with these observations, tissue microarray of human RCC samples has shown the lack of E-cadherin immunoreactivity in VHL-deficient samples (Gervais et al., 2007). This study also found that low Fuhrman grade samples were positive for E-cadherin and VHL immunostaining and had a better prognosis. Conversely, high-grade tumors were negative for E-cadherin and VHL immunoreactivity and had a worse prognosis. However, these observations have been contradicted by another report, which found no association between E-cadherin expression, tumor grade and prognosis in RCC (Ronkainen et al., 2010).

#### 4.5 Glucose transporter-1

Glucose is the major substrate for energy production in mammalian cells. The intracellular transport of glucose and its oxidative metabolism are vital for normal functioning of cells. Intracellular glucose transport is facilitated by a family of 14 glucose transporters (GLUT), of which GLUT-1 is the most studied (Macheda et al., 2005; Ozcan et al., 2007; Suganuma et al., 2007; Lidgren et al., 2008). Due to rapid proliferative rate relative to vascular support of cancer cells, the tumor microenvironment is in a constant state of hypoxia (Ozcan et al., 2007). In order to counteract the deleterious effects of hypoxia, such as apoptosis and necrosis, malignant cells undergo adaptive and genetic changes. One such change is increased uptake of glucose when compared with normal cells through accelerated glycolysis – often referred to as ‘glycolytic switch’ or ‘Warburg effect’ (Warburg, 1956; Airley&Mobasher, 2007; Singer et al., 2011). This is largely mediated by the up-regulation of GLUT especially GLUT-1 (Binder et al., 1997; Smith, 1999; Medina&Owen, 2002; Airley&Mobasher, 2007; Ozcan et al., 2007; Suganuma et al., 2007). It is now well established that accelerated glycolysis and increased glucose uptake mediated by GLUT-1 are the hallmarks of many malignant tumors and that these adaptive changes in glucose metabolism favor survival, proliferation and metastasis of tumor cells, even under hypoxic conditions (Airley&Mobasher, 2007; Ozcan et al., 2007; Singer et al., 2011).

The link between VHL-HIF and GLUT-1 has been well established. GLUT-1 is over-expressed in VHL-mutated mice and the GLUT-1 promoter region has an HRE (Ebert et al., 1995; Park et al., 2007; Lidgren et al., 2008). While the basal level of expression of GLUT-1 in normal PTEC is a subject of debate (Nagase et al., 1995; Ozcan et al., 2007), the over-expression of GLUT-1 in RCC has been demonstrated by many studies (Nagase et al., 1995; Miyakita et al., 2002; Ozcan et al., 2007; Suganuma et al., 2007; Lidgren et al., 2008; Singer et al., 2011). All of these studies concluded that GLUT-1 is over-expressed markedly in clear cell RCC compared with other RCC subtypes, confirming the link between VHL aberration and the subsequent HIF up-regulation. Lactate is one of the byproducts of glycolysis. Due to the enhanced glycolysis, RCC patients are reported to have increased glycolytic enzymes and higher levels of lactate in their serum (Gao et al., 2008). Increased dependence of cancer cells on glycolysis suggests that glycolysis inhibition may be a therapeutic option. Although not well-documented in RCC, experimental glycolysis inhibition has produced anti-cancer effects in certain cancer cell lines (Xu et al., 2005b; Pelicano et al., 2006).

#### 4.6 Carbonic anhydrase IX

CAIX is a membrane-bound glycoprotein belonging to the carbonic anhydrase (CA) family of enzymes and is thought to promote cell proliferation, oncogenesis and tumor progression

in response to hypoxia (Grabmaier et al., 2000; Ivanov et al., 2001; Bui et al., 2003; Lawrentschuk et al., 2011). There are at least 15 isoforms of CA. These enzymes play an important role in the regulation of pH of cells by catalyzing one of the vital reactions of biological systems - the reversible hydration of  $\text{CO}_2$  into bicarbonate and hydrogen ions,  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+$  (Opavsky et al., 1996; Pastorekova et al., 2008; Stillebroer et al., 2010). As discussed above, enhanced glycolysis is a hallmark of cancer cells, which results in accumulation of lactate and a hypoxic acidic microenvironment.  $\text{CO}_2$  is a significant source of hypoxia and acidity in tumors (Pastorekova et al., 2008). Enhanced CAIX expression and the resultant rapid reversible conversion of  $\text{CO}_2$  to  $\text{H}^+$  helps to maintain an acidic, hypoxic microenvironment thereby sustaining tumor progression (Opavsky et al., 1996; Dorai et al., 2006; Pastorekova et al., 2008; Patard et al., 2008; Stillebroer et al., 2010). CAIX is regulated by HIF and the correlation between VHL-HIF-CAIX is well-established (Wykoff et al., 2000; Grabmaier et al., 2004; Patard et al., 2008; Kaluz et al., 2009; Lawrentschuk et al., 2011). Enhanced expression of CAIX has been well documented in RCC (Bui et al., 2003; Zavada et al., 2003; Atkins et al., 2005; Al-Ahmadie et al., 2008; Jensen et al., 2008; Li et al., 2008; Patard et al., 2008; Patard et al., 2009; Stillebroer et al., 2010; Zhou et al., 2010). However, in contrast to other cancers, enhanced CAIX in RCC is associated with a better prognosis. Furthermore, metastatic patients with higher tumoral CAIX expression showed a better response to interleukin-2 treatment (Atkins et al., 2005). Based on the VHL-CAIX status of RCC, Patard and colleagues (Patard et al., 2008) stratified RCC patients into three distinct groups: patients with both VHL mutation and high CAIX expression had the most favourable prognosis; patients with either VHL mutation or high CAIX expression had an intermediate prognosis; and patients with neither VHL mutation nor high CAIX expression had the worst prognosis.

## 5. Promises, pitfalls and future directions

The past decade has witnessed an unprecedented increase in the understanding of molecular mechanisms of RCC, of which, the VHL-HIF pathway arguably is the most explored. Not surprisingly, this has resulted in promising, clinically available novel therapeutic agents. Patients were reported to have progression-free survival with these novel therapeutic agents, and many new drugs are under clinical trial, offering hope for better treatment strategies in the future. However, progression-free survival, which occurs in approximately 10% of selected patients, is generally measured in months, rather than years. Moreover, there is currently no compound, either singly or in combination, which is capable of producing a complete response in metastatic RCC. Systemic toxicity and resistance of RCC in response to currently available VEGF/mTOR inhibitors are starting to emerge. Also, the rising costs of therapy associated with these novel drugs are another barrier to effective treatment. These highlight the need for more effective therapeutic agents for metastatic RCC. One approach would be simultaneous targeting of multiple molecular pathways. Pertinent to the molecular mechanism of VHL-HIF, there are at least 60 HIF-regulated molecules that are engaged in tumor development and progression. This means that targeting the VEGF/mTOR pathway could be potentially abrogated by the opposing actions of numerous molecules favoring tumor progression. Therefore, given the heterogeneity of RCC, individualized, targeted treatment based on a preceding 'molecular map' of each tumor might represent an innovative therapeutic approach to achieving improved clinical outcomes. With the rapid advancements in technology, especially

microarrays and bioinformatics, the availability of clinically feasible platforms to generate molecular maps of individual tumors and customized treatment strategies may become a reality in the near future.

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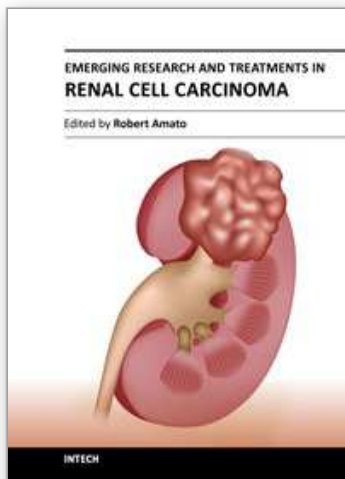
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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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